

$$\frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau = \int_0^t \frac{(t-\tau)^{\alpha-1}}{\Gamma(\alpha)} f(\tau) d\tau$$

positioning a subject having a pulmonary region and a blood circulation path including veins and arteries in an NMR system, the subject's pulmonary region having pulmonary veins and pulmonary arteries and associated vasculature defining a pulmonary portion of the circulation path;

obtaining NMR signal data associated with the polarized ^{129}Xe in the pulmonary region of the subject, the signal data including information corresponding to the polarized gas introduced in said injecting step;

15 identifying the presence of at least one condition of blockage, restriction,
abnormality, and substantially unobstructed free passage of the pulmonary circulation
path.

com
per
vei

3. A method according to Claim 1, further comprising the step of controlling the rate of injection to less than about 3 cc/s at which the injecting step is performed to thereby control the delivery rate of the polarized gaseous ¹²⁹Xe into the vein.

4. A method according to Claim 2, wherein said injected quantity is less than about 20 cc's.

-53-

circulatory path is blocked or restricted based on the presence of polarized ^{129}Xe in the pulmonary arteries.

6. A method according to Claim 1, wherein said obtaining step includes obtaining NMR signal data associated with the presence of gaseous phase polarized ^{129}Xe in the lungs, the image signal intensity of which corresponds to the restriction, blockage or free passage of the pulmonary circulatory path.

16 x 5 A method according to Claim 5, wherein after said injection step, a portion of the injected polarized gaseous polarized ^{129}Xe travels along a portion of the pulmonary circulation path and subsequently enters the lung cavity in a quantity sufficient to provide NMR data with an associated signal intensity, a decreased signal

5 intensity corresponding to the presence of a blockage or restriction in the pulmonary circulation path.

8. A method according to Claim 1, further comprising the step of administering the injection such that the gaseous polarized ^{129}Xe substantially dissolves into the vasculature proximate to the injection site.

Sub 27
A3 526 9. A method according to Claim 8, wherein the controlled injection rate is less than about 2 cc/s.

Sub 27 10. A method according to Claim 1, wherein said injecting step is carried out such that a major portion of the gaseous polarized ^{129}Xe remains substantially as a gas in the bloodstream and exhibits a T_1 in the bloodstream which is greater than about 8 seconds.

11. A method according to Claim 1, wherein said NMR signal data obtaining step is performed in a low magnetic field, wherein the field strength is less than about 0.5T.

11 10 12. A method according to Claim 11, wherein the signal peaks associated

with the ^{129}Xe in plasma and the ^{129}Xe in red blood cells overlap to increase signal intensity associated therewith.

Sub
13. A method according to Claim 1, further comprising the step of introducing a second quantity of a polarized gas to a subject via inhalation during a single imaging session.

14. A method according to Claim 1, wherein said injection step is carried out intravenously.

14 ~~14~~ 13. A method according to Claim ~~14~~ 13, wherein said injection step is carried out via a hypodermic syringe, and wherein said syringe includes gas contacting surfaces which are formed from polarization friendly materials.

15 ~~15~~ 12. A method according to Claim ~~15~~ 12, wherein the second polarized gas comprises ^{129}Xe .

16 ~~16~~ 15. A method according to Claim ~~16~~ 15, wherein said obtaining step includes the steps of:

- 5 exciting and receiving signal data associated with both the first and second quantities of ^{129}Xe with a single transmit/receive excitation coil; and analyzing the NMR signal data associated with said exciting and receiving step in a way which distinguishes gaseous phase ^{129}Xe from the dissolved ^{129}Xe in said image generation step.

Sub
18. A method according to Claim 1, wherein said injection comprises multiple sequential injections thereby allowing for multi-shot MR imaging.

18 ~~18~~ 14. A method according to Claim ~~18~~ 14, wherein the first quantity of polarized ^{129}Xe is isotopically enriched.

Sub
AB 20. A method according to Claim 1, wherein said injected quantity of ^{129}Xe

includes a small amount of CO₂ therewith.

21. A method according to Claim 1, further comprising the step of introducing a quantity of surfactant into a subject proximate to the injection site of the ¹²⁹Xe.

22. A method according to Claim 1, further comprising the step of expelling the ¹²⁹Xe gas from a container into the subject during said injecting step such that the formation of large ¹²⁹Xe gas bubbles are inhibited during said injecting step.

23. A method according to Claim 22, wherein said expelling step configures the bubbles in sizes which are less than about 10 microns in diameter.

24. A method of enhancing the resolution of MRI-based medical images, comprising the steps of:

injecting directly into an injection site associated with a subject a first quantity of polarized ¹²⁹Xe in gaseous form during an NMR imaging session;

5 delivering a second quantity of polarized gas product to the subject within the same imaging session as said injecting step, the second quantity being larger than the first quantity; and

generating an MRI image corresponding to the excitation of the first and second quantities of polarized gas introduced in said injecting and delivering steps.

25. A method according to Claim 24, further comprising the step of introducing a surfactant to the vasculature of a subject such that the surfactant resides proximate to the injected ¹²⁹Xe.

26. A method according to Claim 25, wherein the injection site is associated with a portion of the systemic venous pulmonary vasculature.

27. A method according to Claim 25, wherein the injection site is

associated with a portion of the systemic arterial pulmonary vasculature.

28. A method according to Claim 24, wherein said injecting step is performed by injecting into a vein.

29. A method according to Claim 23, wherein said delivering step is performed by injecting to an artery.

30. A method according to Claim 24, further comprising the step of expelling the polarized ^{129}Xe gas from a container into the subject during said injecting step such that the formation of large ^{129}Xe gas bubbles are inhibited during said injecting step.

31. A method according to Claim 30, wherein said expelling step forms the ^{129}Xe into bubbles in sizes which are less than about 10 microns in diameter.

32. A method according to Claim 24, wherein said delivering step is performed by injecting the second quantity of hyperpolarized gas as a liquid into the subject.

33. A method according to Claim 24, wherein said delivering step is performed by injecting the second quantity of hyperpolarized gas as a gas.

34. A method according to Claim 24, wherein said delivering step comprises the steps of introducing via inhalation to the lungs the second quantity of hyperpolarized gas wherein a portion of the inhaled gas subsequently enters into pulmonary venous vasculature via perfusion uptake into the bloodstream and then subsequently enters the pulmonary vein(s).

35. A method according to Claim 24, wherein said delivering step is carried out via a second injecting step and wherein the first quantity is less than about 20 cc's, and wherein the second quantity is less than about 100 cc's.

36. A method according to Claim 24, further comprising the step of administering the first quantity of polarized ^{129}Xe gas such that it substantially dissolves into the vasculature proximate to the injection site.

37. A method according to Claim 24, further comprising the step of administering the first quantity of polarized ^{129}Xe gas such that it remains substantially non-dissolved in the bloodstream and exhibits a T_1 of at least eight seconds therein.

38. A method according to Claim 24, further comprising the step of processing NMR signal data associated with both said injecting and delivering steps in a manner which distinguishes NMR signal information corresponding to gas phase versus dissolved gas signal information in said MRI image generating step.

39. A method according to Claim 24, further comprising the step of performing said generating step at a low magnetic field strength and acquiring the NMR signal data so that the signal peaks associated with the hyperpolarized ^{129}Xe in the red blood cells and plasma of the blood overlap.

40. A method according to Claim 34, wherein said administering step is carried out at an injection rate which is less than about 2cc/s.

41. A method according to Claim 24, wherein said injected first quantity of ^{129}Xe gas comprises trace amounts of CO_2 .

42. A method of obtaining diagnostic images of the cranial region, comprising the steps of:

injecting less than about 5cc's of ^{129}Xe polarized gas into an injection site in a carotid artery;

5 dissolving said polarized ^{129}Xe gas into the vasculature proximate to the injection site; and

generating an NMR image having signal intensity associated with the NMR excitation of the dissolved injected ^{129}Xe .

43. A method according to Claim 42, wherein said injecting step is performed in a manner which facilitates the dissolution of the gas in the vasculature proximate to the injection site.

44. A method according to Claim 41, wherein said injecting step is carried out in a manner which inhibits the bubble size associated with the injected ^{129}Xe from being larger than about 10 microns in diameter.

45. A method according to Claim 41, further comprising the step of injecting a quantity of a physiologically acceptable surfactant *in vivo* such that it is directed proximate to the injection site.

46. A method of facilitating bubble dissipation associated with the injection of polarized gaseous ^{129}Xe , comprising the step of introducing *in vivo* a physiologically acceptable surfactant temporally proximate to the *in vivo* injection of a quantity of hyperpolarized gas.

47. A method of obtaining an MR image, comprising the steps of:
injecting less than about 100 cc's of gaseous hyperpolarized ^{129}Xe *in vivo* into the vasculature of a mammalian subject; and

5 generating a NMR signal corresponding to the injected quantity of hyperpolarized ^{129}Xe gas.

48. A method according to Claim 46, further comprising the step of administering the injection of the gas into the vasculature so that the gas is substantially dissolved into the vasculature proximate to the injection site.

49. A method according to Claim 46, further comprising the step of administering the injection of the gas into the vasculature so that the gas is

substantially non-dissolved into the vasculature proximate to the injection site.

50. A method according to Claim 47, wherein said injecting step is performed by injecting the hyperpolarized ^{129}Xe into at least one predetermined injection site chosen from the group consisting of a carotid artery, a pulmonary artery, a hepatic artery, and a renal artery.

51. A method according to Claim 47, wherein said injecting step is performed by injecting the hyperpolarized ^{129}Xe gas into at least one injection site chosen from the group consisting of a vein in the arm, a jugular vein, a pulmonary vein, a hepatic vein, and a renal vein.

52. A method according to Claim 47, wherein said injecting step is performed by injecting the hyperpolarized ^{129}Xe into at least two different injection sites, the sites chosen from the group consisting of a carotid artery, a pulmonary artery, a hepatic artery, a renal artery, a vein in the arm, a jugular vein, a pulmonary vein, a hepatic vein, and a renal vein.

53. A method according to Claim 47, wherein said injecting step comprises serially injecting quantities of ^{129}Xe gas during a predetermined imaging period to thereby allow multi-shot imaging.

54. A method according to Claim 47, further comprising the step of injecting a quantity of a physiologically acceptable surfactant *in vivo* such that it is directed proximate to the injected site.

55. A method according to Claim 47, wherein said predetermined injected quantity is less than about 20 cc's.

56. A method according to Claim 47, wherein said injecting step is carried out in a manner which inhibits the bubble size associated with the injected ^{129}Xe from being larger than about 10 microns in diameter.

57. A method according to Claim 47, wherein said injected ^{129}Xe gas comprises trace amounts of CO_2 .

58. A method according to Claim 47, wherein said injecting step comprises directing the hyperpolarized gaseous ^{129}Xe through an intravenous catheter positioned in the vein of a subject.

59. A method according to Claim 58, wherein said directing step comprises directing the hyperpolarized gas through an injector head comprising a plurality of outlet flow orifices formed therein to disperse the hyperpolarized gas into the blood stream of the subject.

60. A method according to Claim 59, further comprising the step of heating the hyperpolarized gas prior to said injecting step.

61. A method according to Claim 58, wherein the injector head includes at least one of a convergent nozzle profile and convergent nozzle orifices.

62. A method according to Claim 59, wherein said directing step comprises directing the hyperpolarized gas such that it flows into a mixing chamber prior to exiting from the injection head orifices.

63. A method according to Claim 58, further comprising the step of adding an emulsifier to the hyperpolarized gas in advance of the injecting step.

64. A method of evaluating the efficacy of targeted drug therapy, comprising the steps of:
delivering a quantity of a predetermined gene treatment preparation or pharmaceutical drug *in vivo* into a mammalian subject having a target site and a treatment condition;

injecting a predetermined quantity of gaseous phase hyperpolarized ^{129}Xe *in vivo* into a mammalian subject such that the hyperpolarized gas is delivered to the target site in gaseous or dissolved form;

generating a NMR image or spectroscopic signal of the target site associated
10 with the injected hyperpolarized ^{129}Xe gas; and

evaluating the NMR image or spectroscopic signal to evaluate the efficacy of the gene treatment or drug on the treatment condition administered in said delivering step.

65. A method according to Claim 64, further comprising the step of acquiring at least two sets of data, the data representing two temporally spaced apart points in time, to evaluate if the treatment condition is influenced by the drug or gene therapy introduced in said delivering step.

66. A method according to Claim 64, further comprising the step of evaluating whether the drug is properly delivered to the target site.

67. A method according to Claim 64, wherein said at least two data sets correspond with a hyperpolarized ^{129}Xe gas NMR signal data acquisition obtained both before said delivering step and after said delivering step.

68. A method according to Claim 65, further comprising at least one of adjusting the quantity or formulation of the drug and confirming the proper delivery to the target site.

69. A method according to Claim 64, wherein the treatment condition is one of cancer, cardiac, renal, hepatic or pulmonary function, and cerebral function, and wherein the target site is selected so as to administer polarized ^{129}Xe gas to a region representative of that condition.

70. A method of determining the presence of cancerous tissue, comprising the steps of:

delivering a quantity of a pharmaceutical drug *in vivo* into a mammalian
subject having a target site associated with a suspect mass or tissue abnormality;
5 injecting a quantity of gaseous hyperpolarized ^{129}Xe *in vivo* into a mammalian
subject such that the hyperpolarized gas is delivered to the target site;
generating a NMR image or spectroscopic signal of the target site
corresponding to the injected hyperpolarized ^{129}Xe gas; and
evaluating the NMR image or signal for the presence or absence of signature
10 patterns in the generated image or signal associated with the presence or absence of
cancer.

71. A method according to Claim 70, wherein the suspect mass is a solid
mass in the breast and said evaluating step determines *in vivo* the presence or absence
of breast cancer.

72. An injectable ^{129}Xe gas product, said ^{129}Xe gas product formulated as a
sterile non-toxic hyperpolarized gas formulation which consists essentially of
isotopically enriched ^{129}Xe in gaseous phase which is injected *in vivo* in a quantity of
less than about 20 cubic centimeters.

73. An injectable ^{129}Xe gas pharmaceutical grade product, said product
formulated as a sterile non-toxic product which consists essentially of ^{129}Xe in
gaseous phase and traces of CO_2 , wherein said injectable gas product is configured to
be dispensed *in vivo*.

74. An syringe, comprising:
a primary gas holding chamber having inner and outer surfaces;
a plunger sized and configured to be received within said primary gas holding
chamber, wherein said plunger has a gas contacting surface;
5 a quantity of hyperpolarized noble gas held in said primary gas holding
chamber;
a valve member operably associated with said primary gas holding chamber;
and

10 a capillary stem positioned intermediate of said plunger and said valve member in fluid communication with said primary gas holding chamber

wherein said primary gas holding chamber includes a wall having outer and inner surfaces, and wherein said primary gas holding chamber inner surface and said plunger gas contacting surface are formed from a material which inhibits contact induced polarization decay associated therewith.

75. A syringe according to Claim 74, further comprising an NMR excitation coil positioned proximate to said gas holding chamber such that in operation it excites the hyperpolarized gas held within said syringe.

76. A syringe according to Claim 74, in combination with a length of conduit and a catheter, wherein said conduit is operably associated with said valve and said catheter is configured to be attached to a subject.

77. A syringe and catheter combination according to Claim 76, wherein said conduit has opposing first and second end portions such that said second end portion is proximate to said syringe gas holding chamber and said first end portion is operably associated with a lumen configured for insertional engagement into the vasculature of a subject to deliver said quantity of hyperpolarized gas thereto.

78. A syringe and catheter combination according to Claim 76, wherein syringe and catheter are operably associated with a delivery path which is configured to form bubbles with diameters which are less than about 150 microns.

79. A method according to Claim 74, wherein said delivery path is configured to form polarized ^{129}Xe gas bubbles with diameters which are less than about 10 μm .

80. A method of preparing a gas container having a sealable gas holding chamber prior to the introduction of a polarized product therein, comprising the steps of:

- 5 (a) evacuating the gas container;
 (b) introducing a quantity of CO₂ gas therein; and
 (c) repeating step (a) after step (b).

81. A method of sizing the length of a capillary stem on a container having a primary hyperpolarized gas holding chamber with a volume, the capillary stem having a volume which is substantially less than that of the gas holding chamber and includes a wall defining a flow channel aperture having a radius or width and a length, the wall having a gas contacting surface formed of a material having a relaxivity value for a selected hyperpolarized gas associated therewith, the method comprising the steps of:

- 10 defining a capillary stem aperture size;
 determining the type of hyperpolarized gas to be held in the container and a diffusion coefficient associated therewith;
 establishing a relaxivity value for the material forming the capillary wall; and
 calculating an optimal capillary stem length.

82. A container having a primary gas holding chamber with a capillary stem, said capillary stem having a length defined by the method of Claim 81.

83. A container, comprising:
 a primary gas holding chamber having a primary volume associated therewith;
 a capillary stem having a wall with a gas contacting surface, a flow aperture, a length, and a capillary volume, said capillary stem in fluid communication with said gas holding chamber, wherein said gas contacting surface of said wall has a relaxivity value for a selected hyperpolarized gas associated therewith; and
 a quantity of hyperpolarized gas held in said gas holding chamber;
 wherein said capillary stem length is selected to substantially correspond to an optimal length to improve the polarization life of the hyperpolarized gas held therein,
 10 and wherein the optimal length is calculated based on a desired T₁, the width of the capillary flow aperture, and the relaxivity value.

84. A container according to Claim 83, wherein said primary chamber volume is about 20cm^3 , said capillary stem width is about 1 mm, said quantity of hyperpolarized gas comprises ^{129}Xe and said capillary stem length is about 4.4cm.

85. A container according to Claim 83, wherein said container has a capillary stem length which is longer when said gas is ^3He than when said gas is ^{129}Xe .

5 86. An injection system for administering polarized gas to a subject, comprising:

a polarized noble gas supply;

a catheter configured and sized for intravenous or intrarterial placement in a subject in fluid communication with the supply of polarized noble gas; and

10 an injection head positioned in a distal portion of the catheter, wherein said injection head comprises multiple orifices having a width of between about 1nm-50 μm , configured so that, in operation, hyperpolarized gas flows therethrough and out of the catheter into the subject.

15 87. An injection system according to Claim 86, wherein said injection head orifices are sized with a width between about 0.01-10 μm .

20 88. An injection system according to Claim 87, wherein said system further comprises an emulsifier source and a mixing chamber positioned intermediate said orifices and said emulsifier and polarized gas sources.

add
A4